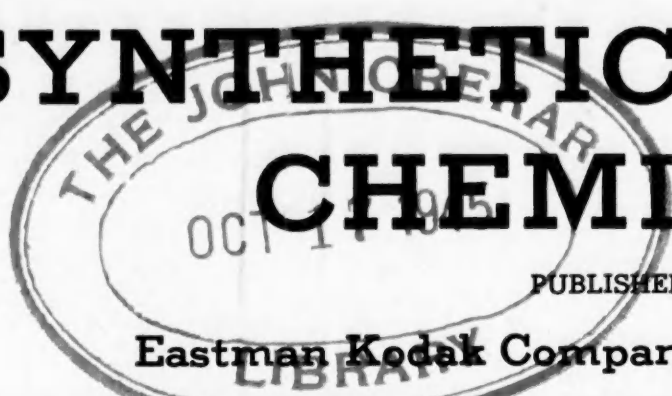


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# SYNTHETIC ORGANIC CHEMICALS



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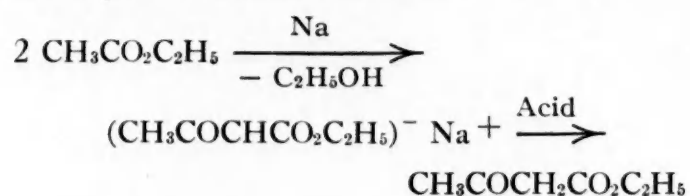
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## Preparation of $\beta$ -Ketoesters

By CHARLES J. KIBLER\*

IN 1863 Geuther treated ethyl acetate with metallic sodium, and isolated ethyl acetoacetate from the reaction mixture. Because of the usefulness of this type of compound, and its versatility in organic syntheses, Geuther's work aroused an interest which has continued without abatement to the present time.

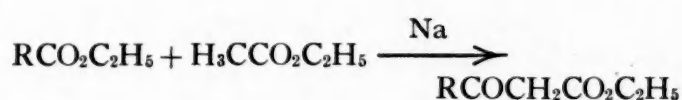
Ethyl acetoacetate, commonly called acetoacetic ester, is the simplest of the class of compounds known as  $\beta$ -ketoesters. It is not a single chemical individual, but rather an equilibrium mixture of two tautomeric forms of the same substance. Acetoacetic ester may be prepared by the action of sodium or other suitable condensing agent on ethyl acetate. This type of reaction is generally known as the Claisen condensation, an example of which follows:



When sodium ethoxide is used as the condensing agent, the reaction quickly reaches equilibrium with relatively low yields of  $\beta$ -ketoester. McElvain (1933) showed that the equilibrium may be displaced in favor of the  $\beta$ -ketoester by fractionally distilling the alcohol as it is

formed. In this manner he succeeded in self-condensing esters of the type  $\text{RCH}_2\text{CO}_2\text{C}_2\text{H}_5$  so as to obtain the corresponding  $\beta$ -ketoesters in excellent yields.

It is also possible to employ two different esters; in this case, it is essential that one ester have a hydrogen atom in the  $\alpha$ -position. Syntheses involving mixed esters are generally more successful if one of the esters has no replaceable hydrogen on the  $\alpha$ -carbon atom. Ethyl benzoylacetate is prepared commercially from ethyl benzoate and ethyl acetate, with sodium as the condensing agent. From the equation

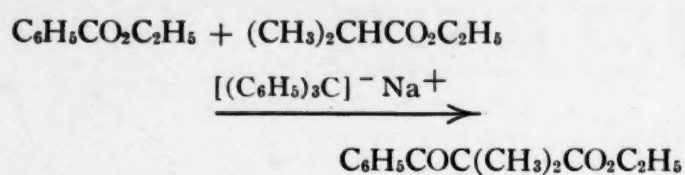


it is obvious that if the first ester had a replaceable hydrogen atom, a mixture of four ketoesters—the two self-condensation products and two mixed ester condensation products—could result. In certain cases, however, one of the latter may predominate.

Until recently it had been possible to prepare, by the Claisen condensation, only those  $\beta$ -ketoesters which have an enolizable hydrogen in the  $\alpha$ -position. In 1937, however, Hauser and Renfrow succeeded in circumventing this limitation by using the strong base sodium triphenylmethyl as the condensing agent. In this way they prepared benzoyldi-

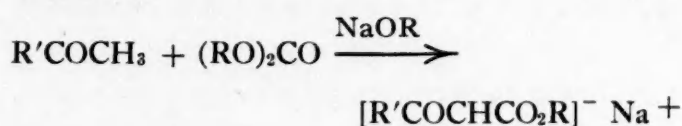
\*Research Laboratories, Eastman Kodak Company, Rochester 4, N. Y.

methylacetic ester from ethyl benzoate and ethyl isobutyrate according to the reaction:



At about the same time, Speilman and Schmidt succeeded in condensing ethyl isobutyrate, using mesitylmagnesium bromide as the condensing agent. Their yield of  $\beta$ -ketoester was somewhat lower than that obtained when sodium triphenylmethyl was employed. The work of these investigators, particularly that of Hauser and his co-workers, has been very fruitful in connection with theoretical considerations of the acetoacetic ester condensations.

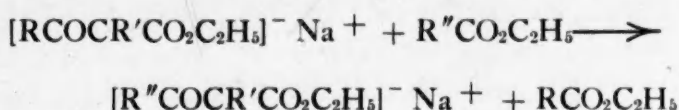
The condensation of ketones and alkyl carbonates with formation of  $\beta$ -ketoesters has been described by a number of workers. From acetophenone and ethyl carbonate, with sodium ethoxide as condensing agent, Claisen (1887) obtained a poor yield of ethyl benzoylacetate. By using a large excess of alkyl carbonate, and removing both the alcohol introduced with the sodium ethoxide and that produced by the reaction, Wallingford, Homeyer, and Jones (1941) have shown that the carbalkoxylation of ketones can be effected in reasonable yield in a large number of cases. The reaction is illustrated below:



It is not limited to methyl ketones, but these give the best yields. Ketones which readily polymerize or undergo self-condensation give unsatisfactory yields.

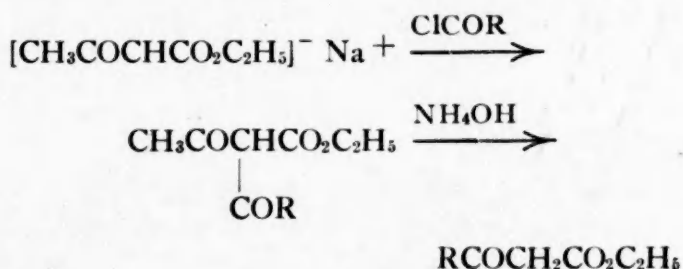
McElvain and Weber (1941) succeeded in preparing various  $\beta$ -ketoesters by an acyl exchange between a  $\beta$ -ketoester and a simple ester. They prepared the sodium salt of acetoacetic ester, which was then treated with excess ethyl benzoate to give ethyl benzoylacetate in

a good yield. The reaction is as follows:



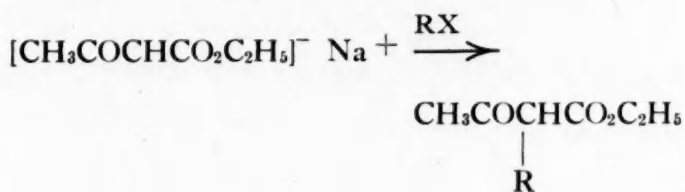
The equilibrium is displaced by the continuous removal of the ester  $\text{RCO}_2\text{C}_2\text{H}_5$  as it is formed. Obviously the reaction proceeds best when R is methyl and R'' is a much larger group, so that the ester,  $\text{RCO}_2\text{C}_2\text{H}_5$ , may be easily fractionated from the reaction mixture. The utility of this synthesis is limited, since it requires a large excess of the ester,  $\text{R}''\text{CO}_2\text{C}_2\text{H}_5$ , which in many cases may be difficult to obtain. If the supply of the latter ester is limited, the first method of preparation cited is preferred.

Another important method of preparing more complex ketoesters from acetoacetic ester is carbon acylation, which is illustrated by the following example:



The sodium salt of acetoacetic ester is acylated with an acyl chloride and the resulting product is selectively hydrolyzed with ammonium hydroxide.

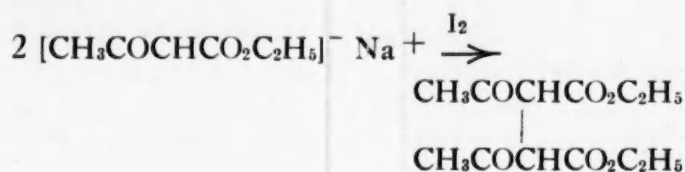
If the sodium salt of a ketoester, such as acetoacetic ester, is treated with an alkyl halide in an inert solvent, the ester is alkylated on the  $\alpha$ -carbon; this is known as carbon alkylation.



Since the product still has a replaceable hydrogen on the  $\alpha$ -carbon, the process may be repeated again to obtain an  $\alpha$ ,  $\alpha$ -dialkyl- $\beta$ -ketoester. When the sodium salt of a  $\beta$ -ketoester is treated with an equivalent of iodine, two molecules are coupled together through the  $\alpha$ -carbon

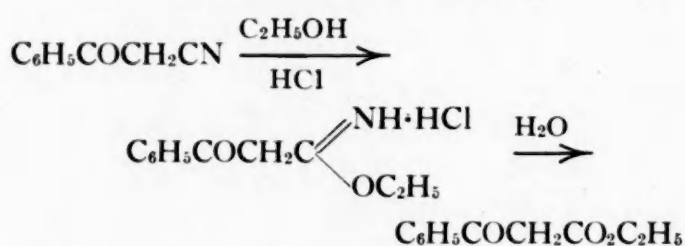


atoms forming diacetosuccinic ester, thus:



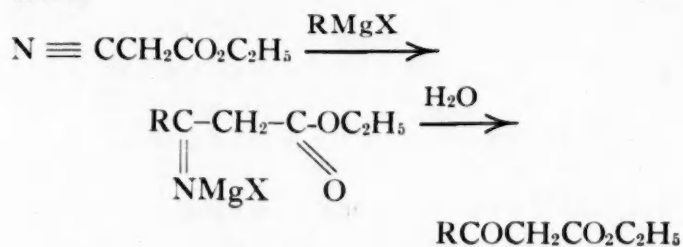
Several syntheses of  $\beta$ -ketoesters have been developed which are not important as general methods but which have been found useful in special cases. Ingrassia (1934) prepared 3,5-dimethylpyrrolylacetate ester in excellent yield from the magnesium derivative of 2,4-dimethyl pyrrole and  $\alpha$ -carbethoxyacetyl chloride.  $\alpha$ -Carbethoxyacetyl chloride also may be condensed with aromatic compounds, using aluminum chloride in a typical Friedel-Crafts reaction, but the yield is poor.

Cyanoacetophenone is converted into benzoylacetate ester by the addition of alcohol to form the iminoether hydrochloride, which is then hydrolyzed to the ester, according to the reaction:



These steps proceed with good yield, and the product obtained is not contaminated with ethyl acetoacetate. If the desired cyanoacetophenone is available, this is a good method of synthesis.

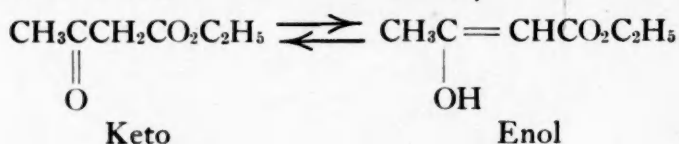
Another method that has been used for preparing  $\beta$ -ketoesters is the reaction of a Grignard reagent with cyanoacetic ester according to the following equation:



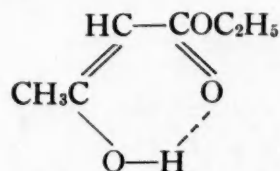
Since the Grignard reagent may also react with the ester group and with the active hydrogen atoms, a mixture of products is obtained.

$\beta$ -Ketoesters may also be prepared by the hydration of  $\alpha$ ,  $\beta$ -acetylenic acids, followed by esterification. The use of the method, however, is somewhat restricted by the limited availability of acetylenic acids.

Our ideas on tautomerism were largely obtained by a study of acetoacetic ester. It was pointed out very early that its behavior in chemical reactions could not be explained by any one formula. Knorr (1911) succeeded in isolating both the enol and keto forms in pure condition by careful crystallization at extremely low temperatures. K. H. Meyer (1911) by chemical analysis, and Auwers (1918) by molecular refraction, established that ordinary liquid acetoacetic ester consists of an equilibrium mixture containing approximately 7% of the enol form. Meyer (1920) observed that when acetoacetic ester is distilled very slowly in a quartz apparatus, the distillate consists



almost entirely of the enol form. A quartz apparatus is necessary because the alkali present in the glass is sufficient to catalyze the interconversion of the tautomers. The fact that the enol form is somewhat more volatile than the keto form is surprising because alcohols generally have higher boiling points than the corresponding ketones. This indicates that the hydroxylic form of acetoacetic ester differs from ordinary alcohols in being unassociated. The lack of association is readily explained by assuming that hydrogen bonding occurs between the hydrogen atom of the enol and the carbonyl group of the ester group as shown:



The hydrogen is then no longer available for bonding with a second molecule.

## A Laboratory Glass Pump

There are many uses for a small pump in a laboratory. Some of the desirable characteristics of a pump are availability, low cost, corrosion resistance, ruggedness, and ease of cleaning. Such a device based on the principle of the air lift or *monté-jus* has been used in the Kodak Research Laboratories for some time.

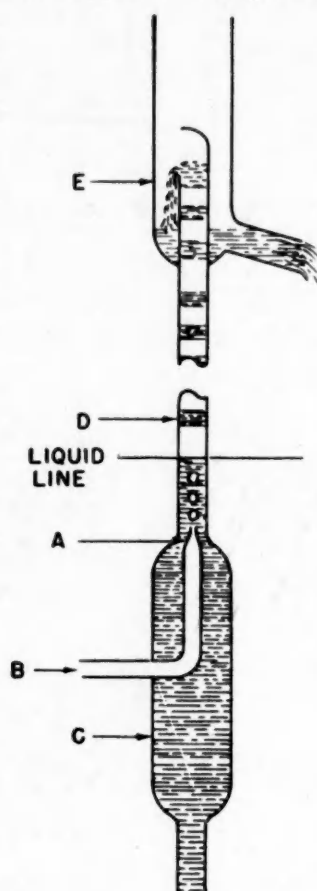
The pump consists essentially of a long glass tube of relatively small diameter containing in its lower section an inner air jet which is submerged in the liquid to be moved. The length of the tube above the air jet is equal to the height to which the liquid is to be raised. A nonessential but useful adjunct is an air separator section at the top.

A typical pump unit is shown in the diagram. The capacity of a pump of this type is proportional to the size of the tubing. A pump having a maximum capacity of about 1.5 liters per minute has the following dimensions: air jet (A) 3 mm., air inlet (B) 6 mm., reservoir (C) 18 mm., tube (D) 12 mm., separator (E) 32 mm. The tube is connected to the pump and the air separator by means of rubber tubing to increase the flexibility

with respect to height and to minimize breakage. When air is applied, the liquid surges intermittently up through the tube.

The whole system can be assembled from straight glass tubing of various sizes used in the manner shown. If glass-blowing facilities are not available, the pump can be assembled by using rubber stoppers to connect the tubing sections.

The pump shown has been used to pump cooling brine through condensers and to circulate a hydrochloric acid solution through a chlorination reaction system. Where oxidation may be a factor, other compressed gases can be used as a source of energy. Other uses and modifications will be obvious to the reader.



## New Eastman Organic Chemicals

P 5567	o-Aminodicyclohexyl (Pract.) BP 118-120°/6mm. ....	1 kg...	\$6.60 E
	$C_6H_{11}C_6H_{10}NH_2$ ...MW 181.31		
P 4562	Benzyl Thiocyanate (Pract.) MP 36-39° .....	1 kg...	3.05 E
	$C_6H_5CH_2SCN$ ...MW 149.20		
5566	1,3-Butanediol BP 205-207° .....	100 g. ...	4.00 C
	$CH_2OHCH_2CHOHCH_3$ ...MW 90.12		
P 5560	1-Chloro-4-pentanone (Pract.) BP 69-71°/17mm. ....	500 g. ...	6.00 D
	$CH_2ClCH_2CH_2COCH_3$ ...MW 120.58		
P 1924	Crotonic Acid (Pract.) MP 70-73° .....	3 kg...	4.95 G
	$CH_3CH:CHCOOH$ ...MW 86.09		
4648	$\alpha$ -Methylstyrene BP 164-165° .....	3 kg...	4.35 G
	$C_6H_5C(CH_3):CH_2$ ...MW 118.17		
5471	iso-Propyl Fumarate BP 108-109°/10mm. ....	1 kg...	8.50 E
	$(CH_3)_2CHOCOCH:CHCOOCH(CH_3)_2$ ...MW 200.23		
5565	L-(-)-Sorbose .....	100 g. ...	6.00 C
	$OCH_2(CHOH)_3COHCH_2OH$ ...MW 180.16		